

CORRESPONDENCE

## Hemophagocytic Lymphohistiocytosis in B-Cell Lymphoproliferative Disorder: Report of a Rare Association

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Dear Editor,

We recently came across an interesting case of a B-cell lymphoproliferative disorder associated with hemophagocytic lymphohistiocytosis.

A 46-year-old female was admitted with 6 month history of high-grade fever, significant weight loss, dyspnea and breathlessness for the past 6 months. There was no preceding medical or surgical history. She had pallor and mild hepatosplenomegaly (liver was palpable 3 cm below right costal margin and spleen 2 cm below left costal margin). There was no palpable peripheral lymphadenopathy. Routine hematological investigations showed anemia (hemoglobin 6.8 g/dl), leucopenia (total leukocyte count 3,000/mm<sup>3</sup>) and thrombocytopenia (platelet count 80,000/mm<sup>3</sup>). Differential leukocyte count revealed neutropenia (polymorphs 35%, lymphocytes 60%, and monocytes 5%) and absolute neutrophil count of 1,050/mm<sup>3</sup>. Peripheral blood film revealed normocytic normochromic red cells with leukopenia and thrombocytopenia. No atypical cells or parasites were noted in the peripheral smear. There was mild impairment of liver function tests (bilirubin 1.8 mg/dl, direct bilirubin 1.2 mg/dl, aspartate transaminase 52 IU/L, alanine transaminase 70 IU/L) and hypertriglyceridemia (triglyceride 350 mg/dl) while renal function tests were within reference ranges. Lactate dehydrogenase level was raised to 850 IU/L.

The patient underwent bone marrow aspiration and trephine biopsy for evaluation of pancytopenia. Bone marrow aspiration and touch imprint smears revealed hypocellular bone marrow fragments composed of normoblastic erythroid precursors, myeloid cells and occasional megakaryocytes. There was histiocytosis with evidence of hemophagocytosis (Fig. 1). No parasites (*leishmania donovani* bodies or plasmodium) were seen.

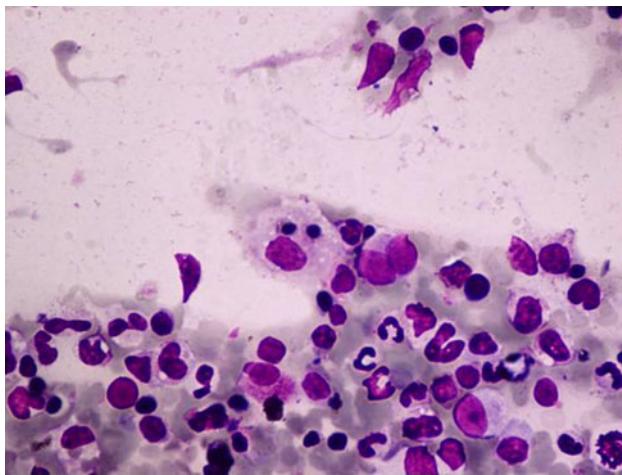
Bone marrow trephine biopsy showed features similar to the bone marrow aspiration and touch preparation. The biopsy was normocellular and showed hemopoietic cells of all three series (Fig. 2a) along with prominent macrophages and hemophagocytosis. In addition, occasional paratrabecular aggregate of lymphoid cells was also seen (Fig. 2b). Special stain revealed grade 2 reticulin fibrosis (Fig. 2c). A presumptive diagnosis of bone marrow infiltration by lymphoma was suggested and further investigations advised. However, her condition deteriorated and she expired 2 days after admission. Immunohistochemistry was performed for CD20 and CD3 on the bone marrow biopsy. The atypical lymphoid cells were positive for CD20 (B-cell marker, Fig. 2d) while CD3 (T-cell marker) showed scattered small lymphocytes. A final pathologic diagnosis of hemophagocytic lymphohistiocytosis with bone marrow infiltration by B-cell non-Hodgkin lymphoma was made.

An autopsy was requested; however the relatives refused permission. Hence, the primary site of lymphoma could not be ascertained.

The standard definition of hemophagocytic lymphohistiocytosis (HLH) requires the presence of at least five of eight criteria to be met: fever, splenomegaly, peripheral cytopenias, hypertriglyceridemia, elevated ferritin (>500 µm/l), elevated soluble CD25, absent NK-cell activity and histological demonstration of HLH in bone marrow, lymph

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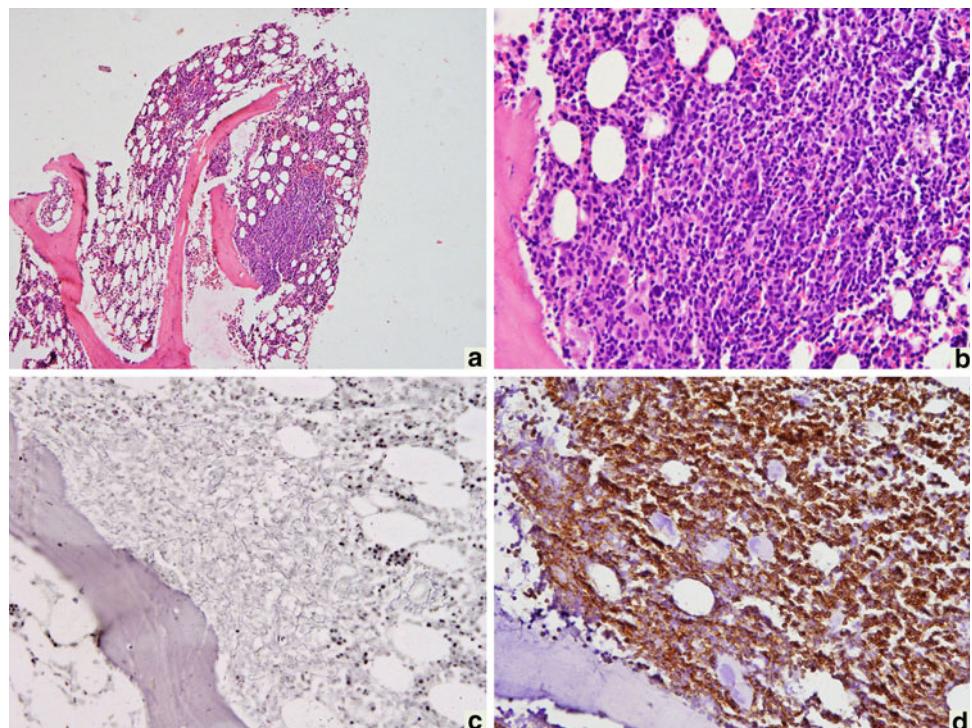
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**Fig. 1** Photomicrograph from the bone marrow aspiration smear showing normoblastic erythroid precursors, myeloid cells and a histiocyte showing hemophagocytosis (Giemsa  $\times 200$ )

nodes or spleen [1]. For a diagnosis of lymphoma-associated HLH, the presence of atypical lymphoid cells should be confirmed histopathologically. In our patient, bone marrow trephine biopsy showed infiltration by atypical lymphoid cells, which stained positive for CD20, hence suggesting infiltration by B-cell lymphoma. Five of the criteria for HLH were also fulfilled (fever, splenomegaly, pancytopenia, hypertriglyceridemia, hemophagocytosis in bone marrow). Hence a diagnosis of lymphoma-associated HLH was made.

**Fig. 2** Photomicrographs of the bone marrow biopsy showing normocellular marrow with a paratrabecular lymphoid aggregate (**a**, H & E  $\times 40$ ). Higher-power view demonstrates the lymphoid nodule to be composed of small to intermediate sized lymphoid cells (**b**, H & E  $\times 200$ ). Stain for reticulin shows increase in reticulin fibers in the marrow (**c**,  $\times 100$ ). Immunohistochemistry for CD20 demonstrates membranous positivity in the lymphoid nodule (**d**,  $\times 200$ )



Inherited HLH, also known as familial HLH or familial erythrophagocytic lymphohistiocytosis, is attributed to defects in perforin or other intracellular pathways required for release of cytolytic granules by NK cells and cytotoxic T cells [2].

The acquired form of HLH has been reported with systemic infections (Epstein-Barr virus, cytomegalovirus, adenovirus, influenza, HIV, parvovirus), inflammatory lesions (juvenile rheumatoid arthritis, lupus erythematosus) and malignancies like lymphomas [2]. The clinical features and diagnostic criteria of acquired HLH are similar to the familial form, except for the family history. Of the lymphomas, T-cell lymphoma and Hodgkin lymphomas have been reported frequently with HLH [3, 4]. T-cell lymphoma-associated HLH usually involves extra-nodal sites like nasal, cutaneous or hepatosplenic locations. A study of T-cell lymphoma-associated HLH revealed elevated lactate dehydrogenase, ferritin, triglycerides and hypofibrinogenemia in the group with HLH as compared to those without HLH. This study showed a significantly worse outcome in T-cell lymphoma with HLH (median survival 40 days vs 8 months in group without HLH) [4].

Rare cases of HLH in association with B-cell lymphoma have also been reported [5–9]. Of the cases reported with B-cell lymphoma, some patients developed HLH during induction or maintenance therapy while others showed HLH at presentation of lymphoma [5–7, 9].

In the present case also, HLH was the presenting feature and the presence of lymphoma was detected on bone

marrow biopsy only. The biopsy showed paratrabecular nodules of lymphoid cells staining positive with CD20 (B-cell marker). The paratrabecular location of the lymphoid aggregates and the merging of the aggregate with the marrow elements were highly suggestive of marrow infiltration by B-cell non-Hodgkin lymphoma. However, the primary site of lymphoma could not be ascertained.

This case is being presented to emphasize that lymphoma associated hemophagocytic lymphohistiocytosis should be considered in patients presenting with fever, pancytopenia, hypertriglyceridemia and hepatosplenomegaly. Bone marrow aspiration and biopsy in such cases assist in a diagnosis of hemophagocytic lymphohistiocytosis as well as marrow infiltration by lymphoma, if present. An accurate diagnosis allows the clinician to institute appropriate chemotherapy and supportive measures and prolong the survival of these patients.

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